Editorial Comment

Cardiac Transplantation—The Need for Prospective, Randomized, Controlled Investigations

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IN THIS ISSUE OF THE WESTERN JOURNAL OF MEDICINE, the aspects of cardiac transplantation that are critical to successful outcomes are discussed succinctly and in depth. Recipient and donor selection, allograft rejection immunoprophylaxis, the treatment of allograft rejection, and the management of infectious and late complications, such as allograft coronary artery disease, have been and remain the key issues of this complex treatment modality for end-stage heart disease. While expertise with the actual surgical procedure is an absolute requisite for success, it is nonetheless inadequate to guarantee short- and long-term survival. Because surgical mortality is less than 1% and the leading causes of death are infection, rejection, and allograft coronary artery disease,[1-4] future progress clearly depends on the refinement of the nonsurgical aspects of cardiac transplantation.

The evolution of cardiac transplantation to its present status as an accepted treatment option in selected patients with end-stage heart disease[5,6] depended on medical and surgical progress from the late 1960s to the present. During that time, most reported studies were from a single institution, were retrospective, and were uncontrolled or historically controlled. Despite these drawbacks, these investigations furthered the science and art of transplantation to the point that survival became routine.[1,2] The lack of randomized, prospective, controlled study methods and other factors, however, have led to a lack of uniformity in immunosuppressive protocols and have generated additional controversies in cardiac transplantation. In this communication, we discuss the complexities, controversies, and issues involved in recipient selection, immunosuppression, and governmental involvement in cardiac transplantation.

Recipient Selection

Due to the disparity between the number of potential recipients and the number of available donor hearts, recipient selection per se raises important societal and ethical concerns.[7] If donor hearts were plentiful, all patients who could benefit from the procedure would be considered for cardiac transplantation. Because a donor organ shortage exists, however, deciding in whom a donor heart should be used involves much more than a simple medical decision; it is a societal responsibility, one that the medical profession must actively participate in discharging. While the medical profession can show feasibility, it cannot unilaterally determine propriety. Should 70-year-old persons be denied transplantation on the basis of age alone because a younger person thereby loses the opportunity for benefit? Should persons with insulin-requiring diabetes be excluded from transplant consideration on the basis of quality-of-life issues even though the procedure would enable longer survival? Answers to these questions involve weighty issues that ethicists, moralists, and others will endlessly debate, and they do indeed require thoughtful consideration by all engaged in cardiac transplantation. Unfortunately, transplant physicians and surgeons cannot stand by, awaiting final, official resolution of donor-recipient ethical issues. Transplant physicians and surgeons must attempt to ensure that recipient selection is neither arbitrary nor inappropriately discriminating and that, in general, accepted candidates will be those in whom the use of scarce donor hearts leads to meaningful life.

Recipient exclusionary criteria have been relaxed in recent years due primarily to improved survival after cardiac transplantation. Criteria that once were absolutely contraindicatory have become only relative contraindications or no longer preclude transplantation.[5,8] The best example of criterion evolution is recipient age. In the early transplant experience, older persons had a higher incidence of morbidity and mortality, and most programs therefore excluded patients older than 45 years.[9-11] As results generally improved, however, older patients began undergoing cardiac transplantation. Recently it has been shown that older patients (up to age 65 years) have survival rates equal to or greater than their younger counterparts.[12,13] Thus, the medical profession has shown the feasibility of transplantation in patients as old as 65 years, and excluding patients from cardiac transplantation simply on the basis of age is not currently supported by the medical literature.

Immunosuppression

Clinical trials of immunosuppressive agents for use in organ transplantation are readily conducted in cardiac transplant recipients because the cardiac allograft lends itself to easier, safer, and more frequent biopsy than renal, hepatic, and pancreatic allografts. Unfortunately, however, prospectively randomized trials in cardiac transplantation are rare, leading each individual center to use different immunosuppressive protocols. The disparity among centers in immunosuppressive protocols is likely to remain until reproducible, appropriately conducted trials are reported.

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ABBREVIATIONS USED IN TEXT

HCFA = Health Care Financing Administration
OPTN = Organ Procurement and Transplantation Network
UNOS = United Network for Organ Sharing

Because the cardiac allograft is amenable to biopsy, it should be possible to individualize recipient immunosuppression to strike the optimal balance in a particular patient with respect to allograft rejection and the risk of infection. The goal of immunoprophylaxis is to administer the lowest amount of immunosuppression that prevents allograft rejection, because any additional immunosuppression exposes the recipient to a higher risk of infection without any benefit.

Immunosuppression for cardiac transplantation can be divided into early prophylaxis, long-term maintenance, and the treatment of established allograft rejection.[14] Early prophylaxis refers to the immunosuppressive therapy given before cardiac transplantation and during the first two to three postoperative weeks. While many programs use T-cell cytolytic therapy (antithymocyte globulin, antilymphoblast globulin, or OKT3 monoclonal antibody), how aggressive early prophylaxis should be is currently debated. The three main purposes of early prophylaxis are the following[14]:

- To prevent or delay rejection during the period of time that the allograft is recovering from the ischemic insult that occurs during donor cardiectomy and recipient implantation because additional graft dysfunction due to rejection at this time might be fatal,
- To minimize the risk that rejection will occur while the recipient is recovering from surgical wounds, and
- To enhance the likelihood of the development of graft tolerance (engraftment) by the host's immune system, thus enabling the patient to be less immunosuppressed.

OKT3 monoclonal antibody may be the best T-cell-active agent in accomplishing all three main purposes of early prophylaxis.[15,16] When compared with antithymocyte globulin in a prospective trial, OKT3 monoclonal antibody not only significantly delayed the first episode of rejection but also decreased the overall number of rejections. Furthermore, early prophylaxis with OKT3 monoclonal antibody enabled the use of significantly lower doses of maintenance corticosteroids long term, to the extent that more than 80% of recipients are maintained without corticosteroids altogether, suggesting that early prophylaxis with this drug enhances graft tolerance.[15,17,18]

OKT3 monoclonal antibody is specific for the heterotrimeric CD3 surface antigen of peripheral T lymphocytes and presumably blocks antigen recognition. Because one mechanism of host recognition of donor antigen may occur by the presentation of donor "passenger" leukocytes to the recipient's reticuloendothelial system, blockade of antigen recognition sites by OKT3 monoclonal antibody until "passenger" leukocytes are cleared from the circulation may reduce the antigen load presented to the recipient.[18]

While long-term maintenance protocols also vary widely, Stevenson and co-workers describe an evolution from prednisone and azathioprine to cyclosporine and prednisone to triple therapy with cyclosporine, azathioprine, and prednisone.[19] Corticosteroid maintenance prophylaxis, however, is associated with many undesirable side effects, and a minimal use of corticosteroids may be desirable. Yacoub and associates were the first to begin using corticosteroid-free maintenance immunosuppression,[20] and it has recently been reported that more than 50% of patients may be successfully weaned completely off corticosteroid maintenance.[17] Patients successfully tapered off corticosteroid maintenance are leaner, less apt to be cushingoid, and less hypercholesterolemic, and they have only half the incidence of infectious complications when compared with recipients who are maintained on corticosteroid therapy.[17,19,21]

Governmental Involvement in Cardiac Transplantation

The federal government has in two ways recently become more involved in cardiac transplantation. First, it has decided to fund cardiac transplantation through the Health Care Financing Administration's (HCFA) Medicare program.[5] The funding of cardiac transplantation for Medicare recipients, while welcomed, has raised important questions regarding what constitutes acceptable results following cardiac transplantation.[6] As expected, no uniform agreement has been reached in the medical community. In response to HCFA's proposed one-year minimal survival rate of 73% for a transplant program to be eligible for Medicare funding, many in the medical community argued for a higher minimum standard, while others argued that a high standard would inhibit clinical progress and make it more difficult for a high-risk patient to receive a needed transplant.[5] It should be noted that patients with severe hemodynamic compromise at the time of transplantation do not appear to have a significantly different survival rate from that of their less hemodynamically compromised counterparts.[6,22,23] Furthermore, it seems unlikely that significant clinical progress will emanate from centers that are unable to achieve one-year actuarial survival rates substantially higher than 73%. While the use of donor hearts in situations in which the chance of meaningful survival is low might be intellectually, academically, or humanistically appealing, this desire must be balanced with the realization that doing so denies the opportunity for benefit to potential recipients in whom the likelihood of success is higher.

Even though HCFA has attempted to define numerically what constitutes a successful program, the overall success of cardiac transplantation as a treatment for end-stage heart disease is best assessed using the intention to treat analysis-of-survival curves. All aspects of cardiac transplantation, including donor heart procurement and allocation, would affect this easily measured variable. A transplant program with a survival following transplantation of 90% but a 70% mortality for recipients awaiting cardiac transplantation has an approximately 27% survival by intention to treat and is less successful than a program that has a 10% mortality in recipients awaiting transplantation and an 80% survival following transplantation, resulting in an approximately 72% survival by intention to treat.

A second aspect of federal involvement in cardiac transplantation emerged when the Congress of the United States established a national Organ Procurement and Transplantation Network (OPTN), under the Public Health Service Act, with the expressed purpose of improving the effectiveness of the nation's renal and extrarenal organ procurement, distribution, and transplantation systems. The OPTN contract was awarded to the United Network for Organ Sharing (UNOS), a private, nonprofit Virginia corporation that has been given the responsibility of accomplishing what professional organizations, individual states, and the nation have been unable

to accomplish since the beginning of clinical organ transplantation: to effect the equitable distribution and effective use of scarce donor organs. Impediments and stumbling blocks to the success of UNOS in accomplishing its charges have come from professional organizations, individual transplant centers, governmental administrative agencies, and congressional delegations and at some point will undoubtedly involve the judicial systems of our nation.

To receive information and advice from the heart transplant community, UNOS, which formerly comprised mostly persons involved in renal transplantation, formed the Heart Transplantation Advisory Committee as a permanent standing committee and assigned individuals from the heart transplantation committee to their Organ Procurement and Distribution Committee and their Membership and Professional Standards Committee. Thus, this private corporation assigned the task of the equitable and effective use of donor hearts has been responsive to the heart transplant community. Whether UNOS will be successful in discharging its responsibility remains to be determined. If UNOS fails, the alternative will be that organ allocation will be regulated by a federal agency that would likely be less responsive to the heart transplant community than UNOS has been.

Conclusion

While many ethical dilemmas remain, cardiac transplantation prolongs life and improves the quality of life. Now that the Stanford University Medical Center and a few other centers have worked out the basics of cardiac transplantation that have resulted in routine survival, it is time to conduct more careful, controlled studies to resolve controversies and advance the art and science of cardiac transplantation further.

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